

## **DETAILED OFFICE ACTION**

In view of the interview with Steven Rider on 17 October, 2011, it was agreed that the instant rejection under 35 USC 112, 1<sup>st</sup> paragraph for lack of enablement should be made as a scope of enablement rejection. In view of this, a supplemental Final Office action is being provided based on the amendments submitted to the claims on 05/02/2011 as a response to the Non-Final Office action mailed 01/05/2011.

Claims 1-44 are pending and stand as filed on 05/02/2011. Claims 39-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Further, claims 8-20, 22, 23, and 27-31 are withdrawn from further consideration as being directed to nonelected species of invention. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/05/2010. Claims 1-7, 21, 24-26, and 32-38 are currently under examination.

### ***Withdrawal of Claim Rejections - 35 USC § 101***

The previous rejection of claims 1-7, 21, 24-26, and 32-38 under 35 USC 101 because the claimed invention is directed to non-statutory subject matter remains withdrawn in view of amendments made to the instant claims.

***Withdrawal of Claim Rejections - 35 USC § 102***

The previous rejection of claims 1 and 32-35, 37 and 38 under 35 U.S.C. 102(e)(2) as being by Hilser et al. remains withdrawn in view of amendments made to the instant claims and in view of the new grounds of rejection set forth below under 35 USC 112, 1st paragraph.

***Withdrawal of Claim Rejections - 35 USC § 103***

The previous rejection of claims 1 and 32-38 under 35 U.S.C. 103(a) as being unpatentable over Hilser et al. in view of Simons et al. remains withdrawn in view of amendments made to the instant claims and in view of the new grounds of rejection set forth below under 35 USC 112, 1st paragraph.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 21, 24-26, and 32-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for providing generalized protein models, does not reasonably provide enablement for generating high resolution three dimensional structures.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use

the invention commensurate in scope with these claims. This rejection has been modified from the previous Office action.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must be able to determine the three dimensional of a protein of unknown structure based only on amide hydrogen-deuterium exchange mass spectroscopy data. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The specification describes the collection of amide hydrogen-deuterium exchange data on proteins and correlating the observed exchange rates of labile hydrogen to secondary structural (two-dimensional) characteristics. The specification does not describe any procedure by which tertiary structural (three-dimensional) characteristics of a protein can accurately or meaningfully derived from using only labile hydrogen position and observed exchange rates with solvent.

c) The specification does not provide any examples wherein "a protein of interest

Art Unit: 1631

of unknown structure" had a three-dimensional structure determined using only the hydrogen-deuterium exchange mass spectroscopy data as instantly claimed. It is further emphasized that applicants arguments filed 05/02/2011 emphasize that the claimed invention "is directed to all the determination of structures of proteins of unknown structure" (emphasis in the original, see page 10, line 9-12 of applicant's response filed 05/02/2011). Rather, the only working example proved in the instant specification involved the concurrent use of X-Ray crystallographic data in conjunction with the hydrogen-deuterium exchange mass spectroscopy data.

d) The nature of the invention, determination of three-dimensional protein structure for proteins of unknown structure, is extremely complex.

e) The prior art does not show that meaningful predictions of three dimensional structure proteins of unknown structure can be determined absent extensive empirical investigations involving a plurality of spectroscopic applications. Ginalski et al. is relied upon for the discussion of protein structure determination protocols and providing a summary of practical lessons for protein structure prediction. It is emphasized therefrom that "(t)heoretically, it should be possible to deduce structure from sequence by accurate simulation of physical processes. We are very far from achieving this goal."

See Ginalski et al., page 1874.

f) The skill of those in the art of protein structure determination is extremely high.

g) The predictability of an arbitrary structure of an unknown protein is not known in the prior art.

h) The claims are broad in that they are drawn to determination of any and all

Art Unit: 1631

proteins of unknown structure, and determining the structure thereof based only on hydrogen and deuterium exchange rate data alone.

The skilled practitioner would first turn to the instant specification for guidance in using the claimed invention. However, the disclosure lacks clear evidence that meaningful three-dimensional structures can be predicted from only hydrogen exchange rate data for observable labile positions in a protein. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not teach that three dimensional structure can be derived from exchange rate data alone. Finally, said practitioner would turn to trial and error experimentation to determine what, if any, meaningful three-dimensional structures can be derived from exchange rate data alone. Such amounts to undue experimentation.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-7, 21, 24-26, and 32-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hisler et al.(US Patent No. 7,027,969) in view of Smith et al. (J Mass SPEC, 1997).

The instant claims are drawn to a method of three dimensional structure prediction. The recited process comprises

Experimentally determining protein amide hydrogen exchange rates via hydrogen-deuterium exchange mass spectrometry, predicting possible structures for the protein, calculating amide exchange rate profiles, comparing calculated amide rates of hydrogen exchange for a set of predicted possible structures based on experimental hydrogen exchange analysis and identifying one or more structures from said set having a calculated exchange rate profile that closely matches the experimental profile. Further recited embodiments include a calculated exchange rate of hydrogen that use thermodynamic parameters for each amino acid in a protein of interest.

Hilser et al. sets forth methods related to predicting pKa of a protein, pH stability of a protein and electrostatic interactions of a protein. Hilser et al. teaches the generation of a plurality of partially folded, ensemble states of a protein of interest (see Hilser et al., col. 1, lines 63-65 and col. 7, lines 28-35). Hilser et al. further teaches the calculation of a protected and exposed regions of a given ensemble structure based on predicted hydrogen exchange rates at each residue position with respect to solvent exposure (see Hilser et al. col. 8, line 9 through 7, lines 3-14 and col. 9, lines 61 through col. 10, line 30). Hilser et al. further teaches that the positions in proteins capable of undergoing observable hydrogen exchange result from known, labile hydrogen positions present in amino acids making up any given protein sequence (see Hilser et al., col. 7, lines 3-26). Hilser et al. further teaches the incorporation of thermodynamic considerations (see Hilser et al., col. 9, lines 25 through col. 10, line 30). Hilser et al.

Art Unit: 1631

further teaches embodiments wherein the above described computational procedure is used to characterize hypothetical structure of ensembles and identifying and designing real world proteins that exhibit the predicted characteristics of said calculated ensembles (see Hilser et al., col. 10, line 35 through col. 12, line 30).

With regard to dependent claim 32, Hilser et al. teaches the use of NMR to obtain experimental hydrogen exchange data (see Hilser et al., col. 1, lines 29-39).

With regard to dependent claim 33-35, Hilser et al. teaches the generation of all possible combinations of ensembles, of incrementally different conformational states, of a protein of interest (see Hilser et al., col. 10, lines 40-54).

With regard to dependent claim 37, Hilser et al. expressly teaches the use of the COREX algorithm (see col. 7, lines 29-35 and col. 8, lines 55 through col. 9, line 24).

While Hilser et al. teaches the above described approaches to generating possible structures, comparing calculated and determined rates of hydrogen exchange for a protein of interest, Hilser et al. does not expressly teach the employment of peptide amide hydrogen-deuterium exchange mass spectrometry.

Smith et al. is relied upon as an in depth review modeling non-covalent structure of protein by amide hydrogen exchange and Mass spectroscopy in a comparative analysis to the quality and use of said data with relation to another protein structure investigative technique that directly measures amide hydrogen exchange rates (i.e. NMR Spectroscopy). See abstract. Smith et al. expressly teaches employment of peptide amide hydrogen-deuterium exchange mass spectrometry in the measurement and back calculation of amide exchange rates as they relate to protein structural

Art Unit: 1631

investigations. See Smith et al. page 136, col. 2, lines 45 through page 142, col 2., line 5. Smith et al. further teaches the employment of the mass spectroscopic analysis and sets forth its use in structure investigation and modeling. See Smith et al., page 142, col. 2, line 6 through page 145, col 2., line 25.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to perform the protein structure and investigations based on protein amide exchange rates as taught by Hilser et a. and incorporate the mass spectroscopic experimental techniques as taught by Smith et al. to obtain amide exchange rates because a practitioner must acquire meaningful amide exchange rate data in order to perform the structural investigations set forth by Hilser et al. and because Smith et al. teaches mass spectroscopy as a viable method for obtaining protein amide exchange rates in this area.

### ***Response to Arguments***

Applicant's arguments filed 05/02/2011 have been considered but are moot in view of the new ground(s) of rejection set forth above.



***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1631

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ERIC S DEJONG/

Primary Examiner, Art Unit 1631